massive quantities of calcium ions; increased movement of the ions through the defective membrane could contribute to the accumulation. In any event, mitochondrial injury could seriously handicap a cell because these structures produce most of the cell's energy.

When the lysosomes incur damage, as they do during ischemia, they release a variety of enzymes that break down cell components, cause inflammation, and further contribute to cellular injury in the affected region of the heart. Investigators have shown that corticosteroids, steroid hormones that suppress inflammation, can stabilize lysosomal and cellular membranes. Braunwald and Maroko found that the hormones have a beneficial effect on infarct size in dogs. However, the results of trials on humans have been inconsistent.

Sobel and his colleagues found that one of these steroids (methylprednisolone) actually increased infarct size and the frequency of dangerous arrhythmias. On the other hand, John Morrison of the North Shore University Hospital in Manhassett, New York, observed that the steroid decreased infarct size in some patients. The reason for this inconsistency is uncertain. Both investigators waited approximately the same time before beginning therapy, and both used a technique devised by the Sobel group to assay for infarct size.

Measuring infarct size in humans continues to be a problem for the investigators engaged in this work. In animal experiments they can directly measure the infarcts in the control and treated animals. When working with humans, the investigators must use noninvasive techniques that will enable them to determine infarct size. In addition, they must show that the infarct is smaller with therapy than it would have been without. Several noninvasive techniques now being developed (*Science*, 3 December) do not yet have the resolution or sensitivity to do this job. Consequently, most groups have used the special electrocardiographic methods developed by Braunwald and Maroko or the enzymatic one devised by Sobel and his colleagues.

The latter method depends on the fact that irreversibly damaged heart cells release an enzyme called creatine phosphokinase into the bloodstream. According to Sobel, an increase in the concentration of the enzyme in blood indicates that a heart attack has occurred and the size of the increase is correlated with the size of the infarct.

The first techniques for measuring creatine phosphokinase activity suffered from a lack of both sensitivity and specificity. Skeletal muscle and other tissues contain structural variants of creatine phosphokinase which catalyze the same reaction as the cardiac enzyme. These variants may be found in blood. The Washington University group has recently developed a radioimmunoassay specific for the heart variant; the new assay is far more sensitive than the previous method, which measured total enzyme activity. (The brain enzyme variant shares a common structure with the one from heart but the brain enzyme does not escape into the bloodstream.) Sobel thinks that the sensitivity of the radioimmunoassay may permit diagnosis of heart attacks earlier than was possible with the older method. Early diagnosis is one of the goals of cardiologists who want to limit infarct size.

—JEAN L. MARX

Homogeneous Catalysis (I): Transition Metal Clusters

Homogeneous catalysis is making an increasingly respectable showing in the real worlds of the chemical and petroleum industries. Although there are now about 20 major industrial processes that use homogeneous catalysts (see box), there are two major obstacles to even wider use of soluble transition metal complexes as catalysts: Such complexes apparently do not catalyze many reactions of the type that are currently of great interest, and the complexes are difficult to separate from the products at the end of the reaction.

The first problem is being attacked by synthesizing complexes that contain three or more atoms of the same metal (polynuclear complexes or metal clusters). To overcome the second, researchers are immobilizing mononuclear complexes on polymer or ceramic supports. At least one process in which metal clusters are used is in an advanced stage of development. (The status of immobilized homogeneous catalysts will be the subject of a second article.) But, for the most part, this attempt to broaden the range of applicability of homogeneous catalysts is still in the laboratory stage.

Homogeneous catalysts are discrete molecules, most often containing a single transition metal atom, in the gas phase or dissolved in solution. Surrounding the metal atom, attached by coordination bonds, are several chemical groups or ligands. A ligand can be an entity as simple as a hydrogen atom, but more often it is a carbon-containing group, such as the carbonyl (CO) or triphenylphosphine [$(C_6H_5)_3P$] groups. For this reason, the catalyst molecules are also known as organometallic complexes. The reactions that they catalyze occur with both the reactants and the catalyst in the same phase. In the case of reactions in solution, the products may remain in solution or may be evolved as a gas.

The vast majority of industrial processes in which catalysts are used rely, however, on solid metal surfaces to catalyze the reaction of gaseous or liquid reactants. Not only do these heterogeneous catalysts enhance the rates of a wide variety of reactions, but, because the metal is in the form of large solid pieces or small particles imbedded in a fixed, porous support material, chemical engineers have little difficulty in devising ways to separate the catalyst from the products in commercial-scale plants.

Heterogeneous catalysts are often not highly selective and thus can be wasteful of reagents. Possibly because the surface of a metal particle exhibits several different crystal orientations, each having a somewhat different catalytic activity for the several reactions possible with a given set of reactants, the catalyst may simultaneously catalyze each of these reactions with a high probability. The loss of a large fraction of reagents in the form of unwanted products is an economic penalty, especially in an age of increasing costs of raw materials.

One reason for considering the use of homogeneous catalysts, therefore, is that, by properly selecting the ligands and the metal atom they surround to have specific electronic and steric properties, chemists can make highly selective catalysts that preferentially promote only one reaction, and thus conserve raw materials. Moreover, in homogeneous catalysts all of the expensive catalyst metal atoms are active, whereas in heterogeneous catalysts most metal atoms are buried beneath the surface of the catalyst and do not contribute to the activity.

Finally, since homogeneous catalysis takes place under milder conditions (lower temperature and pressure) than heterogeneous catalysis does, less energy is consumed in homogeneous processes.

Unfortunately, there are many technologically interesting reactions that researchers have generally been unable to accomplish with homogeneous catalysts. Of particular interest among such reactions are those related to more efficient use of coal, such as coal gasification, coal liquefaction, and conversion of the hydrocarbons and other organic compounds obtainable from coal into more useful forms. Direct synthesis of ammonia and other nitrogen-bearing compounds from atmospheric nitrogen would also be of considerable value.

Over the years, chemists working in heterogeneous catalysis have found that reactions tend to fall into one of two categories: those catalyzed at a single site on the metal surface and those re-

Homogeneous Catalysis and the Real World

Beginning about 25 years ago, interest in homogeneous catalysts—those coexisting with chemical reactants in the same phase (usually liquid)—was itself catalyzed by developments in organometallic chemistry. Although still much the kid brother in the catalysis world, homogeneous catalysts are now used in about 20 important industrial processes including the hydrogenation of olefins (alkenes); hydroformylation of olefins to aldehydes; carbonylation of alcohols to acids; oxidation of olefins to aldehydes, ketones, and vinyl esters; and many polymerization reactions.

Two processes introduced by the Monsanto Company in the early 1970's illustrate the potential of homogeneous catalysts. About 1.1 billion kilograms of acetic acid are manufacturered each year in the United States, primarily as an ingredient for synthesis of other chemicals, such as vinyl acetate. James Roth and his co-workers at Monsanto have devised a homogeneous catalyst based on rhodium complexes that promote the liquid-phase reaction of methanol and carbon monoxide with a selectivity of 99 percent. Consisting of a rhodium atom to which a number of organic carbonyl (CO) ligands are coordinatively bound, the new catalyst obtains such high selectivities even when the carbon monoxide feedstock contains as much as 50 percent hydrogen. Operating at low pressure (15 atmospheres or greater), producing high yields, and requiring less capital investment than previous methods of synthesizing acetic acid, Monsanto's acetic acid process will soon be used worldwide. Licensing agreements have been a significant source of revenue for the company, which has also become a major acetic acid producer itself. The company's plant at Texas City, Texas, manufactures about 140 million kilograms of acetic acid per year.

The amino acid L-dopa [3-(3,4-dihydroxyphenyl)-L-alanine] is used to relieve the symptoms of Parkinson's disease in hundreds of thousands of sufferers of the shaking palsy. As an optically active compound, L-dopa rotates the polarization of plane-polarized light passing through it, and it has a twin molecule, D-dopa, which rotates the polarization in the opposite direction. Conventional methods of direct chemical synthesis produce equal amounts of both optical isomers, which must then be separated, because only L-dopa is of use as a drug. Separation is an expensive proposition because, apart from their optical activities, the isomers have identical physical properties.

William Knowles and his associates at Monsanto have devised a homogeneous catalyst, based on complexes similar to the molecule tris(triphenylphosphine)chlororhodium $\{Rh[P(C_6H_5)_3]_3Cl\}$, that promotes the formation of a precursor of synthetic L-dopa with a better than 90 percent selectivity. The selectivity results from substituting certain ligands in place of the phenyl groups to create asymmetric (and thereby optically active) ligands around the rhodium in the catalyst complex. As with the catalyst for the acetic acid process, the asymmetric catalyst has become dominant in its field. It and others like it are expected to become of great importance in the future for the synthesis of drugs, food additives, and other optically active chemicals.

Interest in homogeneous catalysts peaked around 1970, and since then chemists have been discovering the limitations of soluble transition metal complexes. One of the limitations is that many reactions that have become of great interest since the arrival of the energy crisis have so far resisted homogeneous catalysis. Heterogeneous processes exist, but have not yet proved economical, except in special circumstances. Such reactions include the production of "synthesis gas" (carbon monoxide and hydrogen) from coal, production of liquid hydrocarbons and alcohols from synthesis gas, restructuring of hydrocarbons, reduction of atmospheric nitrogen, and activation of oxygen for use in direct oxidation processes or in fuel cells.

Recently, however, some progress has begun to be made. At the University of Texas, Rowland Pettit and his associates have observed the production of methanol when carbon monoxide and water react in the presence of $Fe(CO)_5$ or $Cr(CO)_6$ complexes. Research is at an early stage with many problems yet to be solved, such as the evolution of considerable quantities of hydrogen gas and formic acid in addition to methanol.

Although John Bercaw and his co-workers at the California Institute of Technology did not find catalytic activity, they did observe the stoichiometric reduction of carbon monoxide by hydrogen to produce methanol. In a stoichiometric reaction, the species that would normally be the catalyst is not regenerated at the end of the reaction but is consumed as one of the reactants. A series of three reactions successively involving carbonyl and hydride complexes of bis(pentamethylcyclopentadienyl)zirconium $\{[\eta^5\text{-}C_5(CH_3)_5]_2Zr\}$ was required to effect methanol production. They are a first step toward a homogeneous catalyst.

And, at the University of Wisconsin, Charles Casey and Stephen Neumann have recently found a new way to synthesize transition metal formyl compounds of the general formula $L_xM(OCH)$, where L is one of a number of organic ligands and M is a transition metal. Such compounds are thought to be intermediate species in the reduction of carbon monoxide by hydrogen, as catalyzed in heterogeneous processes. The production of these species and the subsequent study of their homogeneous reactions may greatly aid in understanding how to design homogeneous catalysts for energy-related reactions.—A.L.R.

quiring the assistance of several sites on the surface working together to promote the reaction. Consisting of a single metal atom, homogeneous catalysts—not surprisingly—are most effective in the former category.

Although some progress is being made in the use of the traditional mononuclear homogeneous catalysts to drive reactions of the multisite type, some researchers are studying polynuclear metal clusters (Fig. 1). They hope that several adjacent metal atoms will act something like the surface of a bulk metal and, at the same time, will retain the advantages of homogeneous catalysts in the areas of selectivity and mild operating conditions. Conversely, the details of what happens during catalysis on a metal surface are notoriously hard to unravel; hence some chemists hope to use metal clusters, which can be studied by such techniques as x-ray diffraction, nuclear magnetic resonance, and infrared spectroscopy, to model the catalytic action of metal surfaces.

Chemists have been learning how to synthesize and determine the structure of metal cluster complexes for many years, but it is much more recently that their attention has been directed toward the catalytic properties of these entities. Earl Muetterties of Cornell University has argued that metal cluster complexes might be more effective than mononuclear complexes in catalyzing reactions that involve breaking strong bonds, such as the triple bond in carbon monoxide. For catalysis to take place, the reactant molecules must bind to the metal atoms. If a molecule such as carbon monoxide were bound to the metal cluster so that the carbon formed a bond with one metal atom in the cluster and the oxygen formed a bond with a second metal, then the net effect would be to increase the carbon-oxygen bond distance. The increased bond distance would, in turn, make the carbon monoxide much more susceptible to reduction by a second reactant, such as hydrogen. In this way, for example, the reduction of carbon monoxide from coal by hydrogen to produce methane or methanol could be catalyzed.

Muetterties, Renato Ugo of Milan University, and Jack Norton of Princeton University are among those who have pointed out that surfaces of heterogeneous catalysts have a number of properties that cannot possibly be duplicated by mononuclear homogeneous catalysts but which have been shown to exist in polynuclear clusters, thus suggesting some similarity between the two structures.

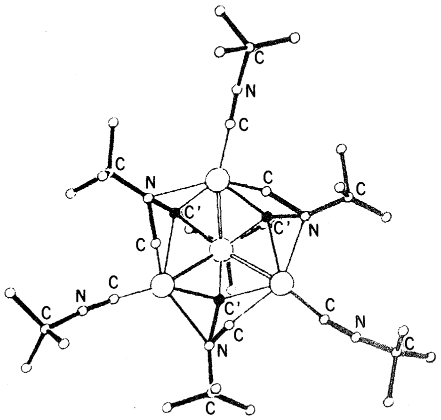

Fig. 1. Perspective drawing of the $Ni_4[CNC(CH_3)_3]_7$ molecule. The molecule is viewed along its idealized threefold axis and normal to its triangular base. Nickel atoms are represented by large, open circles. Small open circles marked C designate coordinated carbon atoms of the isocyanide ligands. Small blackened circles marked C′ designate carbon atoms that serve a different structural function. Small unmarked open circles are CH_3 groups. [Source: Earl Muetterties, Cornell University]

First, as mentioned previously, reactants can bind to more than one metal atom of a heterogeneous catalyst. Several examples of metal clusters have now been found in which organic ligands are bound to more than one metal atom in the cluster. Second, investigators have strong evidence for the migration of chemisorbed ligands over metal surfaces. Corresponding to ligand migration is the scrambling of hydrogen and carbonyl ligands in rhodium clusters that have been observed in nuclear magnetic resonance studies with carbon-13 isotopes. Finally, Norton and K. J. Karel of Princeton have observed interactions between the metal atoms in the cluster $Ir_4(CO)_{12}$ when triphenylphosphine ligands are substituted for the carbonyl at each metal site. These investigators found that the rate at which triphenylphosphine replaced carbonyl at one iridium site depended on whether substitutions at other sites had or had not occurred previously.

Several examples of catalysis apparently due to polynuclear metal cluster homogeneous catalysts have been reported. Closest to being commercialized is a process for producing ethylene glycol ($HOCH_2CH_2OH$) developed by Roy Pruett and his co-workers at the Union Carbide Chemicals and Plastics Division, South Charleston, West Virginia. The Union Carbide researchers use a rhodium carbonyl metal cluster of an undisclosed composition to homogeneously catalyze the reaction of carbon monoxide and hydrogen. In the still unoptimized process, ethylene glycol accounts for about 65 to 70 percent of the products. Methanol and glycerine account for the remainder.

According to Pruett, the driving force behind development of the rhodium cluster catalyst is the possibility of using cheaper and more versatile alternative raw materials to produce ethylene glycol. Carbon monoxide and hydrogen mixtures are available as the synthesis gas derived from coal, heavy or light petroleum fractions, natural gas, or garbage. In the existing process, a silver heterogeneous catalyst and ethylene starting material are used. Operation of a commercial-scale plant, in which the new process will be used, is scheduled for the early- to mid-1980's.

Recently, Peter Ford, Robert Rinker, and Richard Laine of the University of California at Santa Barbara observed the catalysis of the water-gas shift reaction ($H_2O + CO \rightarrow H_2 + CO_2$) when a ruthenium cluster [$Ru_3(CO)_{12}$] was added to an alkaline alcoholic solution. The water-gas shift reaction is used to vary the ratios of carbon monoxide and hydrogen in synthesis gas to those needed for synthesis of such products as ammonia, methanol, or substitute natural gas.

Over a 30-day period, a total of 150 moles of hydrogen gas was evolved per mole of catalyst at 1 atmosphere of carbon monoxide and at 100°C. The catalytic activity increased rapidly at higher temperatures. The investigators were not able to identify the active catalytic species, but infrared spectroscopy experiments indicated the presence of polynuclear hydride species, such as $H_4Ru_4(CO)_{12}$ and $H_2Ru_4(CO)_{13}$.

Muetterties and his colleagues at Cornell have also demonstrated catalysis of such reactions as conversion of acetylene to benzene with nickel clusters $\{Ni_4[CNC(CH_3)_3]_7\}$, reduction of carbon monoxide with hydrogen to produce methane using iridium or osmium clusters [$Ir_4(CO)_{12}$ or $Os_3(CO)_{12}$], and conversion of hydrocarbons from one form to another by breaking and re-forming carbon-carbon or carbon-hydrogen bonds with the aid of ionic clusters containing no ligands, such as Bi_5^{3+}. In all reactions, the observed catalytic activity was rather low; the significance of these reactions lies in the observation of catalytic activity due to homogeneous polynuclear clusters. For example, Muetterties, Michael Thomas, and Barbara Beier of Cornell obtained only about 1 percent conversion in the reduction of carbon monoxide as promoted by the iridium catalyst after 5 days of operation at 140°C and a pressure of about 2 atmo-

(Continued on page 1202)

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spheres, but the sole product was methane (100 percent selectivity).

A major difficulty in interpreting the results of all homogeneous catalyst experiments is identification of the active catalytic species. Spectroscopic measurements can determine whether certain species are present, but lengthy and complicated studies of reaction mechanisms, in which the intermediate species of what may be a multiple-step reaction are sorted out for each step, are needed to unequivocally identify the catalyst entity. Metal clusters are no exception to this difficulty and are further complicated by the tendency of some clusters to fragment into mononuclear complexes under reaction conditions. It is difficult to prove that catalysis is not due to unobserved but very active complexes of this type present in unobservably small concentrations. A second worry is that microscopic specks of pure metal in the form of a colloidal suspension could also be the active (in this case heterogeneous) species.

From the point of view of the engineer interested in an efficient, economical process, perhaps it does not matter what the active species is, so long as one knows what starting materials to use. Researchers find this an unsatisfactory attitude. Muetterties and his colleagues, for example, have found in their studies of nickel clusters that they do indeed fragment. But careful identification of intermediate species led to the conclusion that it was the polynuclear not the mononuclear species that was active. Laser light scattering experiments indicated the absence of suspended particles.

John Shapley and his associates at the University of Illinois prefer to minimize the fragmentation problem as much as possible. They are, therefore, concentrating on the use of third-row transition metals (rhenium, osmium, and iridium). Shapley believes that the metal-metal bonds between these elements are strong enough to resist fragmentation, whereas the bonds between metals such as the first-row transition elements are much weaker and thus subject to easy rupturing.

At the University of Alabama, Tuscaloosa, Charles Pittman and Robert Ryan are trying to build clusters that cannot fragment without completely destroying the complex, thus ensuring that no mononuclear complexes could exist. The Alabama researchers have begun experiments with a first-row transition metal (cobalt) and have synthesized the polynuclear complex $Co_4(CO)_8(\mu^2\text{-}CO)_2(\mu_4\text{-}PC_6H_5)_2$, which is said to behave in this way. With this structure, they have observed the catalysis of several hydrocarbon reactions involving the breaking and re-forming of carbon-carbon and carbon-hydrogen bonds.

Because so much catalysis research occurs in industrial laboratories and is therefore frequently proprietary, it is difficult to judge how soon metal cluster catalysts will appear in operating chemical plants or how large their impact will be. From all accounts, however, industrial activity, if not feverish, is certainly widespread. Thus, as access to inexpensive raw materials becomes more restricted in the years ahead, if a way exists to make clusters work, it will likely be found.—ARTHUR L. ROBINSON

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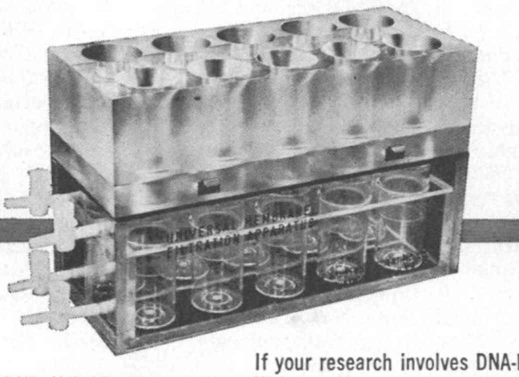

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